Recombinant production of therapeutic proteins provides huge benefits to human health and promises solutions to some of the most devastating and currently untreatable diseases in healthcare. Key to the development of new therapeutic proteins is to optimize and engineer living cells, namely cell factories, to produce therapeutic proteins by taking advantage of the cells protein production machinery. However, there is an insufficient understanding of the cellular processes and their regulatory mechanisms that hinder optimal therapeutic protein production such as cell growth, protein productivity and product quality. Our successes are dependent on getting a better understanding of the biological processes that comprise the cell factory, and the ability to directly engineer the cell factory for beneficial production of both new and existing therapeutic products. In this thesis, the development of a number of novel tools is reported that aim to accelerate the construction of production cell lines for therapeutic proteins with optimal phenotypic attributes for industrial processes. Chinese hamster ovary (CHO) cells are the predominant production host for therapeutic proteins, and are the cell factory of interest in this thesis. The core of the thesis is revolved around the development and application of genome editing techniques that enable us to precisely engineer the genome of CHO cells by either rendering specific-targeted genes unfunctional or inserting new genes in precise genomic locations. This allows us to i) facilitate improved studies of gene functions, ii) remove cellular traits that are disadvantageous to protein production, iii) control and predict the level and stability of protein expression, and iv) design and engineer new cellular functions. Overall, the results of this thesis illustrate the benefits of advancing the toolbox for designing and engineering CHO cell lines. Each chapter demonstrates direct applications of strategies to improve the therapeutic production capabilities of CHO cell factories, with the goal to speed up the development process of new therapeutic proteins and reducing the costs in order to benefit a broader range of patients around the globe.

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